IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

IN RE: '318 PATENT INFRINGEMENT LITIGATION	))))	C.A. No. 05-356-KAJ (consolidated)

NOTICE OF DEPOSITION AND SUBPOENA OF MITSUI & CO (USA), INC. PURSUANT TO FEDERAL RULE OF CIVIL PROCEDURE 45

PLEASE TAKE NOTICE that, pursuant to Rule 45 of the Federal Rules of Civil Procedure, plaintiffs Janssen Pharmaceutica N.V., Janssen, L.P. and Synaptech, Inc. (collectively, "Janssen") will take the deposition upon oral examination of Mitsui & Co (USA), Inc. at the offices of Esquire Deposition Services, 216 E. 45th Street, 8th Fl., New York, NY 10017-3304, beginning at 9:00 A.M. on June 23, 2006.

NOTICE IS FURTHER GIVEN THAT the deposition will be recorded stenographically through instant visual display of testimony (real-time), by certified shorthand reporter and notary public or such other person authorized to administer oaths under the laws of the United States, and shall continue from day to day until completed. This deposition will be videotaped.

NOTICE IS FURTHER GIVEN THAT Mitsui & Co (USA), Inc. is instructed to produce documents, identified in the attached Subpoena, at the offices of Esquire Deposition Services, 216 E. 45th Street, 8th Fl., New York, NY 10017-3304 by 9:00 A.M. on June 16, 2006.

NOTICE IS FURTHER GIVEN THAT pursuant to the Federal Rules of Civil Procedure, Janssen will serve upon Mitsui & Co (USA), Inc. a Subpoena in a Civil Case. Attached hereto as Exhibit A is a true and correct copy of that Subpoena.

ASHBY & GEDDES

/s/ Tiffany Geyer Lydon

Steven J. Balick (I.D. #2114)
John G. Day (I.D. #2403)
Tiffany Geyer Lydon (I.D. #3950)
Lauren E. Maguire (I.D. #4261)
222 Delaware Avenue, 17th Floor
P.O. Box 1150
Wilmington, DE 19899
(302) 654-1888

Attorneys for Janssen Pharmaceutica N.V., Janssen, L.P., and Synaptech, Inc.

Dated: June 2, 2006

170132.1

EXHIBIT A

A088 Subpoena in a Civil Case

Issued by the

United States District Court

SOUTHERN DISTRICT OF NEW YORK

IN RE: '318 PATENT INFRINGEMENT LITIGATION

SUBPOENA IN A CIVIL CASE

Case Number:[1] C.A. No. 05-356-KAJ (consolidated)
(District of Delaware)

TO: Mitsui & Co (USA), Inc.
200 Park Avenue
New York, NY 10166-0130

☐ YOU ARE COMMANDED to appear in the United States District court at the place, date, and time specified below to testify in the above case.

PLACE OF TESTIMONY	COURTROOM
	DATE AND TIME

☒ YOU ARE COMMANDED to appear at the place, date, and time specified below to testify at the taking of a deposition in the above case. Please See Schedule A Attached

PLACE OF DEPOSITION Recording Method: By stenographer and videotape	DATE AND TIME
Esquire Deposition Services, 216 E. 45th Street, 8th FL, New York, New York 10017-3304	June 23, 2006 at 9:00 A.M.

☒ YOU ARE COMMANDED to produce and permit inspection and copying of the following documents or objects at the place, date, and time specified below (list documents or objects): Please See Schedule B Attached

PLACE	DATE AND TIME
Esquire Deposition Services, 216 E. 45th Street, 8th FL, New York, New York 10017-3304	June 16, 2006 at 9:00 A.M.

☐ YOU ARE COMMANDED to permit inspection of the following premises at the date and time specified below.

PREMISES	DATE AND TIME

Any organization not a party to this suit that is subpoenaed for the taking of a deposition shall designate one or more officers, directors, or managing agents, or other persons who consent to testify on its behalf, and may set forth, for each person designated, the matters on which the person will testify. Federal Rules of Civil Procedure, 30(b)(6).

ISSUING OFFICER'S SIGNATURE AND TITLE (INDICATE IF ATTORNEY FOR PLAINTIFF OR DEFENDANT)	DATE AND TIME
Attorney for Plaintiffs Janssen Pharmaceutica N.V., Janssen L.P., and Synaptech, Inc.	June 2, 2006
ISSUING OFFICER'S NAME, ADDRESS AND PHONE NUMBER Tiffany Geyer Lydon, Ashby & Geddes 222 Delaware Avenue, 17th Floor Wilmington, DE 19899 Tel: 302-654-1888	

(See Rule 45, Federal Rules of Civil Procedure, Parts C&D on next page)

[1] If action is pending in district other than district of issuance, state district under case number.

PROOF OF SERVICE

DATE PLACE

SERVED

SERVED ON (PRINT NAME) MANNER OF SERVICE

SERVED BY (PRINT NAME) TITLE

DECLARATION OF SERVER

I declare under penalty of perjury under the laws of the United States of America that the foregoing information contained in the Proof of Service is true and correct.

Executed on _____
DATE

_____
SIGNATURE OF SERVER

_____
ADDRESS OF SERVER

Rule 45, Federal Rules of Civil Procedure, Parts C&D

(c) PROTECTION OF PERSONS SUBJECT TO SUBPOENAS.

(1) A party or an attorney responsible for the issuance and service of a subpoena shall take reasonable steps to avoid imposing undue burden or expense on a person subject to that subpoena. The court on behalf of which the subpoena was issued shall enforce this duty and impose upon the party or attorney in breach of this duty an appropriate sanction which may include, but is not limited to, lost earnings and reasonable attorney's fee.

(2)(A) A person commanded to produce and permit inspection and copying of designated books, papers, documents or tangible things, or inspection of premises need not appear in person at the place of production or inspection unless commanded to appear for deposition, hearing or trial.

(2)(B) Subject to paragraph (d)(2) of this rule, a person commanded to produce and permit inspection and copying may, within 14 days after service of subpoena or before the time specified for compliance if such time is less than 14 days after service, serve upon the party or attorney designated in the subpoena written objection to inspection or copying of any or all of the designated materials or of the premises. If objection is made, the party serving the subpoena shall not be entitled to inspect and copy materials or inspect the premises except pursuant to an order of the court by which the subpoena was issued. If objection has been made, the party serving the subpoena may, upon notice to the person commanded to produce, move at any time for an order to compel the production. Such an order to comply production shall protect any person who is not a party or an officer of a party from significant expense resulting from the inspection and copying commanded.

(3) (A) On timely motion, the court by which a subpoena was issued shall quash or modify the subpoena if it

(i) fails to allow reasonable time for compliance,

(ii) requires a person who is not a party or an officer of a party to travel to a place more than 100 miles from the place where that person resides, is employed or regularly transacts business in person, except that, subject to the provisions of clause (c)(3)(B)(iii) of this rule, such a person may in order to attend trial be commanded to travel from any such place within the state in which the trial is held, or

(iii) requires disclosure of privileged or other protected matter and no exception or waiver applies, or

(iv) subjects a person to undue burden

(3)(B) If a subpoena

(i) requires disclosure of a trade secret or other confidential research, development, or commercial information, or

(ii) requires disclosure of an unretained expert's opinion or information not describing specific events or occurrences in dispute and resulting from the expert's study made not at the request of any party, or

(iii) requires a person who is not a party or an officer of a party to incur substantial expense to travel more than 100 miles to attend trial, the court may, to protect a person subject to or affected by the subpoena, quash or modify the subpoena, or, if the party in who behalf the subpoena is issued shows a substantial need for the testimony or material that cannot be otherwise met without undue hardship and assures that the person to whom the subpoena is addressed will be reasonably compensated, the court may order appearance or production only upon specified conditions.

(d) DUTIES IN RESPONDING TO SUBPOENA.

(1) A person responding to a subpoena to produce documents shall produce them as they are kept in the usual course of business or shall organize and label them to correspond with the categories in the demand.

(2) When information subject to a subpoena is withheld on a claim that it is privileged or subject to protection as trial preparation materials, the claim shall be made expressly and shall be supported by a description of the nature of the documents, communications, or things not produced that is sufficient to enable the demanding party to contest the claim.

SCHEDULE A

DEFINITIONS

1. "Synaptech" shall mean Plaintiff Synaptech, Inc., Synaptec, Inc., and all of Synaptech, Inc., its corporate parents, corporate predecessors and past or present subsidiaries, affiliates, divisions, departments, officers, directors, principals, agents and employees including without limitation Bonnie M. Davis, M.D. and Synaptec, Inc.

2. "Dr. Bonnie Davis" refers to Bonnie M. Davis, M.D., holder of United States Patent No. 4,663,318.

3. "You," "your," "yours," or "Mitsui" shall mean Mitsui & Co. (USA), Inc. and all of Mitsui & Co (USA), Inc.'s corporate parents, corporate predecessors and past or present subsidiaries, including and without limitation to Mitsui Pharmaceuticals, Inc. or its corporate successor Nihon Schering KK, affiliates, divisions, departments, officers, directors, principals, agents, employees and any individuals or entities that at any time have acted or purported to act on behalf of Mitsui & Co. (USA), Inc.'s or its successors.

4. "Communication" and "communications" mean any contact, transmission, or exchange of information between two or more persons, verbally or in writing or by any other means.

5. "Concerning" means relating to, referring to, regarding, describing, being evidence of, constituting, memorializing, or reflecting in any way.

6. "Document" means the complete original (or complete copy where the original is unavailable) and each non-identical copy (where different from the original because of notes made on the copy or otherwise) of any writing or record, including but not limited to all written, typewritten, handwritten, printed or graphic matter of any kind or

nature, however produced or reproduced, any form of collected data for use with electronic data processing equipment, and any mechanical or electronic visual or sound recordings, including, without limitation, all tapes and discs, now or formerly in your possession, custody or control, including all documents as defined in the broadest sense permitted by the Federal Rules of Civil Procedure. The term "document" includes, but is not limited to, e-mails, invoices, purchase orders, checks, receipts, letters and other correspondence, offers, contracts, agreements, bids, proposals, licenses, permits, reports to government agencies, ledgers, accounts receivable, accounts payable, account statements, financial statements, monthly reports, other reports, minutes of meetings, sales estimates, sales reports, memoranda, notes, calendar or diary entries, agendas, bulletins, graphs, charts, maps, photographs, drawings, surveys, data, price lists, summaries, telegrams, teletypes, computer printouts, magnetic tapes, discs, microfilm, and microfiche.

7. "Person" and "persons" mean any natural person and any business, legal, corporate, or governmental entity, association, or organization.

8. "Alzheimer's Disease" means any diagnosis, illness, or ailment described as being of the Alzheimer's type, including without limitation Senile Dementia of the Alzheimer's Type, and/or Alzheimer's Dementia.

9. "'318 patent" means United States Patent No. 4,663,318 attached hereto as Exhibit 1.

10. "Galantamine" includes without limitation galantamine, galanthamine, and any salt of galatamine, such as galantamine hydrobromide.

11. In these Requests, the present tense includes the past and future tenses, the connectives "and" and "or" shall be construed either disjunctively or conjunctively as

necessary to bring within the scope of the Request all responses that might otherwise be construed to be outside of its scope, the singular shall include the plural and vice versa, "all" shall include "any" and vice versa, and "each" shall include "every" and vice versa, all to the end that each Request shall be construed to cover the broadest scope of information.

TOPICS

1. The names and responsibilities of all persons who were involved in any evaluation, consideration or discussion by or on behalf of Mitsui, to market or develop the '318 patent and the contributions made by them in any evaluation, consideration or discussion by or on behalf of Mitsui to license, market or develop the '318 patent.

2. The names and responsibilities of all persons who were involved in any evaluation, consideration, or discussion by or on Mitsui of galantamine as a treatment for Alzheimer's Disease, and the contributions made by them in any evaluation, consideration or discussion by or on behalf of Mitsui of galantamine as a treatment for Alzheimer's Disease.

3. All negotiations or communication by or on behalf of Mitsui and Synaptech or Dr. Bonnie Davis regarding the '318 patent.

4. All negotiations or communication by or on behalf of Mitsui and Synaptech or Dr. Bonnie Davis regarding galantamine as a treatment for Alzheimer's Disease.

5. The October 13, 1987, letter from Fukuichi Oka, General Manager, New Product Planning for Mitsui Pharmaceuticals, Inc. to Dr. Bonnie Davis, attached hereto as Exhibit 2, and copied to Mr. M. Hattori (Mitsui & Co., New York), including without limitation the meaning of, basis for, and any evaluation or analysis concerning the statement set forth in the letter that "[w]e highly appreciate your research activity and are much desirous

of finding of possibilities of co-operating with you for developing such your new compounds and obtaining their license in Japan."

6. The Secrecy Agreement executed by Fukuichi Oka and Bonnie M. Davis, and attached hereto as Exhibit 3.

7. The April 28, 1988, letter from Takafumi Kitano, Ph.D., Manager of the New Product Planning Department for Mitsui Pharmaceuticals, Inc., attached hereto as Exhibit 4 and copied to Mr. Hattori, Mitsui & Co., New York, including without limitation the meaning of, basis for, and any evaluation or analysis concerning the statement set forth in the letter that "[Mr. Kitano] ha[d] already transmitted to our research people for their first step evaluation."

8. November 2, 1988, letter from Bonnie M. Davis, M.D. to Takafumi Kitano, PH.D., Manager of New Product Planning Department for Mitsui Pharmaceuticals, Inc., attached hereto as Exhibit 5, and copied to Mr. Hattori, Mitsui & Co., New York, including without limitation the meaning of, basis for, and any evaluation or analysis concerning the statement set forth in the letter that "discussions concerning the licensing of galanthamine are in progress."

9. The February 3, 1989, letter from Takafumi Kitano, Ph.D., attached hereto as Exhibit 6, and copied to Mr. M. Hattori, Mitsui & Co., New York, including without limitation the meaning of, basis for, and any evaluation or analysis concerning the statement set forth in the letter that "its is generally believed that regarding such sort of drugs there is quitely [sic] poor relation between animal data and clinical efficacy in patients with Alzheimer's disease and therefore, clinical studies of such drugs bring to us a difficulty of

estimation of our research and development schedule and expense to proceed with the further development."

10. The February 3, 1989, letter from Takafumi Kitano, Ph.D., attached hereto as Exhibit 6, and copied to Mr. M. Hattori, Mitsui & Co., New York, including without limitation the meaning of, basis for, and any evaluation or analysis concerning the statement set forth in the letter that "they are afraid that unexpected adverse effects may occur in patients during a long term treatment because of a similarity of its chemical structure to codein."

11. Any evaluation or analysis conducted by or on behalf of Mitsui concerning galantamine as a treatment for Alzheimer's Disease.

12. All communications or discussions between Mitsui & Co. (USA), Inc. and Mitsui Pharmaceuticals, Inc. concerning the '318 patent or galantamine as a treatment for Alzheimer's Disease.

13. All communications or discussions between you and any other person regarding the '318 patent.

SCHEDULE B

Pursuant to Rule 45 of the Federal Rules of Civil Procedure, Plaintiffs Janssen Pharmaceutica N.V., Janssen, L.P., and Synaptech, Inc. hereby propound this subpoena on Bristol-Meyers Squibb Company. This subpoena calls for you to produce the documents described under the heading "Requests for Production of Documents" below, in accordance with the following "Definitions" and "Instructions."

DEFINITIONS

Notwithstanding any definition set forth below, each word, term, or phrase used in these Requests is intended to have the broadest meaning permitted under the Federal Rules of Civil Procedure. The following definitions and rules on construction apply to the Requests:

1. "Synaptech" shall mean Plaintiff Synaptech, Inc., Synaptec, Inc., and all of Synaptech, Inc., its corporate parents, corporate predecessors and past or present subsidiaries, affiliates, divisions, departments, officers, directors, principals, agents and employees including but not limited to Bonnie M. Davis, M.D.

2. "Dr. Bonnie Davis" refers to Bonnie M. Davis, M.D., holder of United States Patent No. 4,663,318.

3. "You," "your," "yours," or "Mitsui" shall mean Mitsui & Co. (USA), Inc. and all of Mitsui & Co (USA), Inc.'s corporate parents, corporate predecessors and past or present subsidiaries, including and without limitation to Mitsui Pharmaceuticals, Inc. or its corporate successor Nihon Schering KK, affiliates, divisions, departments, officers, directors,

principals, agents, employees and any individuals or entities that at any time have acted or purported to act on behalf of Mitsui & Co. (USA), Inc.'s or its successors.

4. "Communication" and "communications" mean any contact, transmission, or exchange of information between two or more persons, verbally or in writing or by any other means.

5. "Concerning" means relating to, referring to, regarding, describing, being evidence of, constituting, memorializing, or reflecting in any way.

6. "Document" means the complete original (or complete copy where the original is unavailable) and each non-identical copy (where different from the original because of notes made on the copy or otherwise) of any writing or record, including but not limited to all written, typewritten, handwritten, printed or graphic matter of any kind or nature, however produced or reproduced, any form of collected data for use with electronic data processing equipment, and any mechanical or electronic visual or sound recordings, including, without limitation, all tapes and discs, now or formerly in your possession, custody or control, including all documents as defined in the broadest sense permitted by the Federal Rules of Civil Procedure. The term "document" includes, but is not limited to, e-mails, invoices, purchase orders, checks, receipts, letters and other correspondence, offers, contracts, agreements, bids, proposals, licenses, permits, reports to government agencies, ledgers, accounts receivable, accounts payable, account statements, financial statements, monthly reports, other reports, minutes of meetings, sales estimates, sales reports, memoranda, notes, calendar or diary entries, agendas, bulletins, graphs, charts, maps, photographs, drawings, surveys, data, price lists, summaries, telegrams, teletypes, computer printouts, magnetic tapes, discs, microfilm, and microfiche.

7. "Person" and "persons" mean any natural person and any business, legal, corporate, or governmental entity, association, or organization.

8. "Alzheimer's Disease" means any diagnosis, illness, or ailment described as being of the Alzheimer's type, including without limitation Senile Dementia of the Alzheimer's Type, and/or Alzheimer's Dementia.

9. "'318 patent" means United States Patent No. 4,663,318 attached hereto as Exhibit 1.

10. "Galantamine" includes without limitation galantamine, galanthamine, and any salt of galatamine, such as galantamine hydrobromide.

11. In these Requests, the present tense includes the past and future tenses, the connectives "and" and "or" shall be construed either disjunctively or conjunctively as necessary to bring within the scope of the Request all responses that might otherwise be construed to be outside of its scope, the singular shall include the plural and vice versa, "all" shall include "any" and vice versa, and "each" shall include "every" and vice versa, all to the end that each Request shall be construed to cover the broadest scope of information.

INSTRUCTIONS

1. The response to each Request shall include all documents within your possession, custody, or control. The phrase "possession, custody, or control" means a document in your physical custody; or, that you own in whole or in part; or, have a right by contract, statute or otherwise to use, inspect, examine or copy on any terms; have an understanding, express or implied, that you may use, inspect, examine or copy on any terms; or you have, as a practical matter, the ability to use, inspect, examine or copy such document.

2. If any document or tangible thing that would have been responsive to the Requests below has been destroyed or is no longer in your possession, custody or control, you shall serve upon the undersigned counsel for the Plaintiff a written list that (i) identifies each such document by date, author or preparer, and addressee(s); and (ii) states the date of, and identity of the person responsible for, its destruction, loss, transfer, or other action by which the document or tangible thing left your possession, custody or control.

3. The response to each Request shall state, with respect to each item or category, that inspection and related activities will be permitted as requested, unless the Request is objected to, in which event the reasons for objection shall be stated. If objection is made to part of an item or category, the part shall be specified. Any such objection shall not extend the time within which you must otherwise answer or respond to a Request to which no specific objection has been made.

4. If you contend that an otherwise discoverable document would be excludable from production, state the reasons for such objection or grounds for exclusion and identify each person having knowledge of the factual basis, if any, on which the objection or ground is asserted.

5. If any document that would have been responsive to any of the Requests below is not produced because of a claim of privilege or immunity, you shall serve upon the undersigned counsel for the Plaintiff a written list that (i) identifies each such document by date, author or preparer, and addressee(s); (ii) identifies the name and position of each person to whom a copy was furnished, and each person to whom the original or a copy was shown; (iii) states the general subject matter of each document; (iv) identifies the Request to which the withheld document is responsive; and (v) states the ground on which each document is asserted to be privileged or immune from disclosure. Any attachment to an allegedly privileged or immune document shall be produced unless you contend that the attachment is also privileged or immune, in which case the information specified in the previous sentence shall be separately provided for each such attachment.

6. If there is any question as to the meaning of any part of these Requests, or an issue as to whether production of responsive documents would impose an undue burden, counsel for the Plaintiff should be contacted promptly.

7. You may produce legible, complete, and exact copies of the original documents, provided that the originals be made available for inspection upon request by counsel for the Plaintiff.

8. You are requested to respond in writing to the following Requests, and produce the requested documents for inspection and copying, at the time, date, and location set forth in the subpoena.

REQUESTS FOR PRODUCTION OF DOCUMENTS

1. All documents concerning any evaluation, analysis, consideration or discussion to license, market or develop the '318 patent or a '318 patent product.

2. All documents concerning any evaluation, analysis, consideration, or discussion of galantamine as a treatment for Alzheimer's Disease.

3. All documents concerning communications or discussions between you and Synaptech or Dr. Bonnie Davis regarding the '318 patent.

4. All documents concerning communication between you and Synaptech or Dr. Bonnie Davis regarding galantamine as a treatment for Alzheimer's Disease.

5. All documents concerning the October 13, 1987, letter from Fukuichi Oka, General Manager, New Product Planning for Mitsui Pharmaceuticals, Inc. to Dr. Bonnie Davis, attached hereto as Exhibit 2, and copied to Mr. M. Hattori (Mitsui & Co., New York), including without limitation the meaning of, basis for, and any evaluation or analysis concerning the statement set forth in the letter that "[w]e highly appreciate your research activity and are much desirous of finding of possibilities of co-operating with you for developing such your new compounds and obtaining their license in Japan."

6. All documents concerning the Secrecy Agreement executed by Fukuichi Oka and Bonnie M. Davis, and attached hereto as Exhibit 3.

7. All documents concerning the April 28, 1988, letter from Takafumi Kitano, Ph.D., Manager of the New Product Planning Department for Mitsui Pharmaceuticals, Inc., attached hereto as Exhibit 4 and copied to Mr. Hattori, Mitsui & Co., New York, including without limitation the meaning of, basis for, and any evaluation or analysis

concerning the statement set forth in the letter that "[Mr. Kitano] ha[d] already transmitted to our research people for their first step evaluation."

8. All documents concerning the November 2, 1988, letter from Bonnie M. Davis, M.D. to Takafumi Kitano, PH.D., Manager of New Product Planning Department for Mitsui Pharmaceuticals, Inc., attached hereto as Exhibit 5, and copied to Mr. Hattori, Mitsui & Co., New York, including without limitation the meaning of, basis for, and any evaluation or analysis concerning the statement set forth in the letter that "discussions concerning the licensing of galanthamine are in progress."

9. All documents concerning the February 3, 1989, letter from Takafumi Kitano, Ph.D., attached hereto as Exhibit 6, and copied to Mr. M. Hattori, Mitsui & Co., New York, including without limitation the meaning of, basis for, and any evaluation or analysis concerning the statement set forth in the letter that "its is generally believed that regarding such sort of drugs there is quitely [sic] poor relation between animal data and clinical efficacy in patients with Alzheimer's disease and therefore, clinical studies of such drugs bring to us a difficulty of estimation of our research and development schedule and expense to proceed with the further development."

10. All documents concerning the February 3, 1989, letter from Takafumi Kitano, Ph.D., attached hereto as Exhibit 6, and copied to Mr. M. Hattori, Mitsui & Co., New York, including without limitation the meaning of, basis for, and any evaluation or analysis concerning the statement set forth in the letter that "they are afraid that unexpected adverse effects may occur in patients during a long term treatment because of a similarity of its chemical structure to codein [sic]."

11. All documents concerning any communication or discussion between Mitsui & Co. (USA), Inc. and Mitsui Pharmaceuticals, Inc. concerning the '318 patent or galantamine as a treatment for Alzheimer's Disease.

12. All documents concerning any communication or discussion between you and any person concerning the '318 patent or galantamine as a treatment for Alzheimer's Disease.

EXHIBIT 1

United States Patent [19]
Davis

[11] **Patent Number: 4,663,318**
[45] **Date of Patent: May 5, 1987**

[54] **METHOD OF TREATING ALZHEIMER'S DISEASE**

[76] Inventor: **Bonnie Davis**, 17 Seacrest Dr., Huntington, N.Y. 11743

[21] Appl. No.: **819,141**

[22] Filed: **Jan. 15, 1986**

[51] Int. Cl.[4] **A61K 31/55**
[52] U.S. Cl. **514/215**
[58] Field of Search 514/215

[56] **References Cited**

PUBLICATIONS

Chem. Abst. (81)–72615z (1974).
Chem. Abst. (86)–115157z (1977).
Horshenson et al. J. Med. Chem. vol. 29, No. 7, 7/86, pp. 1125–1130.
Kendall et al., J. Chem. & Hospital Pharmacol., (1985) 10-327-330.
S. Chaplygina et al., J. of Highest Nervous Activity vol. XXIV 1976 Issue 5, pp. 1–4.
Krause, J. of Highest Nervous Activity, vol. XXII, 1974, Issue 4.

Primary Examiner—Stanley J. Friedman
Attorney, Agent, or Firm—Ladas & Parry

[57] **ABSTRACT**

Alzheimer's disease may be treated with galanthamine.

7 Claims, No Drawings

METHOD OF TREATING ALZHEIMER'S DISEASE

GENERAL FIELD OF THE INVENTION

The present invention relates to a novel method of treating Alzheimer's disease and more particularly to a treatment using galanthamine.

BACKGROUND ART

Galanthamine and acid addition salts thereof have, for many years, been known to have anticholinesterase properties. Cozanitis in Anaesthesia 29 163–8 (1974) describes the effect of galanthamine hydrobromide on plasma cortisol of patients receiving relaxant anaesthesia and Cozanitis et al in Acta Anesth. Scand. 24:166–168 (1980) describe the effect of galanthamine on plasma ACTH values during anaethesia. These studies showed an increase in both plasma cortisol and plasma ACTH when galanthamine was administered to patients together with atropine.

Il'yuchenok et al (Chemical Abstracts 70 36296K describe the appearance of θ-rhythm on an electroencephalogram when galanthamine is administered intravenously to rabbits.

Increase in short-term memory in dogs by use of galanthamine is described by Krauz in Chemical Abstracts 81 72615Z.

The antagonistic effect of galanthamine to scopolamine-induced amnesia in rats is described by Chaplygina et al in Chemical Abstracts 86 115157Z, and in Zhurnal Vysshei Nervnoi Deiatelnosti imeni P. Pavlova (MOSKVA) 26:1091-1093, 1976.

Alzheimer's disease, presenile dementia, causes much distress not only to those suffering from the disease, but also those who are close to them. The custodial care of advanced victims of the disease is a tremendous expense to society. At present, there is no effective means of improving the functional status of persons with the disease.

It is an object of the present invention to improve the cognitive function of patients with Alzheimer's disease.

SUMMARY OF THE INVENTION

A method for treating Alzheimer's disease and related dementias which comprises administering to mammals, including humans, an effective Alzheimer's disease cognitively-enhancing amount of galanthamine or a pharmaceutically-acceptable acid addition salt thereof. A radioactively-labelled form of the molecule may also serve as a diagnostic test for Alzheimer's disease.

DETAILED DESCRIPTION OF THE INVENTION

Galanthamine can be administered in any convenient chemical or physcial form. For example, it may be administered as its hydrobromide, hydrochloride, methylsulfate or methiodide.

Galanthamine or its pharmaceutically-acceptable acid addition salts may be administered to a patient suffering from Alzheimer's disease orally or by subcutaneous or intravenous, injection, or intracerebroventricularly by means of an implanted reservoir. It may be necessary to begin at lower doses than are ultimately effective.

Galanthamine and its acid addition salts form crystals. They are in general only sparingly soluble in water at room temperature and so injectible compositions are normally in the form of an aqueous suspension. If necessary, pharmaceutically-acceptable suspension aids may be employed. Typically, such a suspension will be employed at a concentration of 1–50 mg/ml more commonly 5–40 mg/ml, for example, 5–30 mg/ml or 10–40 mg/ml, typically 20–30 mg/ml of galanthamine. Typical dosage rates when administering galanthamine by injection are in the range 5–1,000 mg per day depending upon the patient. For example, divided doses in the range 0.5–5 mg/kg body weight per day may prove useful. Typically, one might administer a dosage of 50–300 mg per day to a patient of a body weight of 40–100 kg, although in appropriate cases such dosages may prove useful for patients having a body weight outside this range. In other cases, dosages as low as 10 mg and as high as 500 mg may be appropriate for persons in this body weight range.

Galanthamine or its pharmaceutically-acceptable acid addition salts may also be administered orally, for example, as an aqueous suspension or a solution in aqueous ethanol or as a solid such as a tablet or capsule. Suspensions or solutions for oral administration are typically of about the same concentration as those used for injections. However, it may be desirable when administering the drug orally to use a higher dosage rate than when administering it by injection. For example, dosages up to 2000 mg per day may be used, such as dosages in the range 100–600 mg per day. In preparing such tablets or capsules, standard tablet or capsulemaking techniques may be employed. The dosage rate of galanthamine or its pharmaceutically-acceptable salt will normally be in the same range as for oral administration of a liquid. If desired, a pharmaceutically-acceptable carrier such as starch or lactose may be used in preparing galanthamine tablets. Capsules may be prepared using soft galatine as the encapsulating agent. If desired, such capsules may be in the form of sustained release capsules wherein the main capsule contains microcapsules of galanthamine which release the contents over a period of several hours thereby maintaining a constant level of galanthamine in the patient's blood stream.

The following test provides a good animal model for Alzheimer's disease in humans: A selective lesion is placed in a subcortical nucleus (nucleus basalis of Meynert) with a resultant cortical cholinergic deficiency, similar in magnitude to that seen in early to moderate stage Alzheimer's disease. Numerous behavioral deficits, including the inability to learn and retain new information, characterizes this lesion. Drugs that can normalize these abnormalities would have a reasonable expectation of efficacyin Alzheimer's disease. Haroutunian, V, Kanof P, Davis, KL: Pharmacological alleviations of cholinergic-lesion-induced memory defects in rats. Life Sciences 37:945–952, 1985.

The following specific formulations may find use in treatment of Alzheimer's disease:

Tablets or capsules containing 5, 10 and 25 mg galanthamine hydrobromide to be taken four times a day, or a sustained-release preparation delivering an equivalent daily dose.

Parenteral solution containing 5 mg/ml.

Liquid formulation for oral administration available in 5 mg/5 ml and 25 mg/5 ml concentration.

There have been reports that galanthamine can cause cardiac arrythmias. In such cases, it may be desirable to

administer galanthamine in conjunction with another drug such as propanthelinbromide to control such arrythmias.

I claim:

1. A method of treating Alzheimer's disease and related dementias which comprises administering to a patient suffering from such a disease a therapeutically effective amount of galanthamine or a pharmaceutically-acceptable acid addition salt thereof.

2. A method according to claim 1, wherein the administration is parenteral at a daily dosage of 5–1,000 mg of galanthamine or a pharmaceutically-acceptable acid addition salt thereof.

3. A method according to claim 2, wherein said dosage rate is 50–300 mg per day.

4. A method according to claim 1, wherein said administration is oral and is in the range 10–2000 mg per day.

5. A method according to claim 4, wherein said dosage rate of 100–600 mg per day.

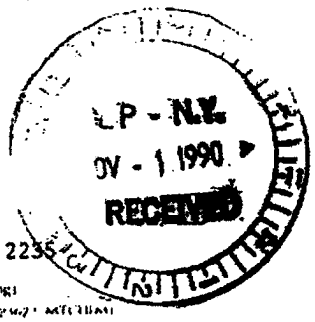
6. A method according to claim 1, wherein galanthamine is administered at a dosage rate of 0.1 to 4 mg/kg body weight of a patient, parenterally.

7. A method according to claim 1, wherein galanthamine is administered intracerebroventricularly via an implanted reservoir at a dosage rate of 0.01 to 5.0 mg/kg day.

* * * * *

EXHIBIT 2

MITSUI PHARMACEUTICALS, INC.
● 12-2, Nihonbashi 3-chome Chuo-ku Tokyo, 103 Japan ● (The 6th floor of Asahi Building)
● Telephone(Tokyo) 274-4711 ● Cable Mitsuipharm Tokyo ● Telex 0722 [illegible]



Our Ref. No. 2235

October 13, 1987

Dr. Bonnie Davis
Seacrest Drive 17
Huntington
N.Y.
U. S. A.

Dear Dr. Davis,

This correspondence is the first contact with you. Enclosed please find herewith the pamphlet of our company.

We have noted in recent patent publications that you have developed various interesting compounds such as mentioned below.

(1) Agents for the treatment of Alzheimer type dementia ;
Galanthamine and its derivatives:

Japanese unexamined pat. publication No. 1987-215527(1987.9.22)
Jpn. pat. application No. 1987-7684 (1987.1.16)
US pat. appl. No. 1986-819141 (1986.1.15)

and so on.

We highly appreciate your research activity and are much desirous of finding of possibilities of co-operating with you for developing such your new compounds and obtaining their license in Japan.

Therefore, we are very pleased, if you would kindly send us more detailed (if possible, at first, non-confidential or published, and secondly confidential) information on preclinical and clinical data of your licensable products so that we can study and evaluate them. Of course, we are ready to sign a secrecy agreement, if necessary, for receiving such information from you.

...Cont'd

MITSUI
PHARMACEUTICALS, INC.

Our Ref. No. 2235

We are generally interested in psychotropic, cardiovascular, anticancer, immunomodulatory and diagnostic agents field. So if you have any other licensable agent other than the above patented compounds, please be kindly requested to introduce it to us.

By the way, we may contact you hereafter, also through Mr. Masayuki Hattori, Assistant General Manager, Technical Development Center, Mitsui & Co., New York.

We thank you very much for your kind attention and are looking forward to hearing from you at your earliest convenience.

With best regards,

Yours sincerely,

MITSUI PHARMACEUTICALS, INC.

Fukuichi Oka
General Manager
New Product Planning

Enclosure : Pamphlet of MITSUI PHARMACEUTICALS, INC.

c.c.: Mr. M. Hattori (Mitsui & Co., New York)
Mr. A. Sudo (Mitsui & Co., Tokyo)

EXHIBIT 3

SECRECY AGREEMENT

This AGREEMENT, made this day of 1987, by and between Dr. B. Davis (hereinafter referred to as "DAVIS "), and Mitsui Pharmaceuticals,Inc. of 12-2, Nihonbashi 3-chome Chuo-ku Tokyo, 103 JAPAN (hereinafter referred to as "MITSUI").

WITNESSETH

WHEREAS, DAVIS possesses certain confidential trade secret information, data, and know-how relating to a product described as Galanthamine hydrobromide an agent for the treatment of Alzheimer's disease ("PRODUCT"); and

WHEREAS, MITSUI wishes to receive said confidential trade secret information, data, and know-how for the purpose of evaluating same to determine its commercial interest therein; and

WHEREAS, DAVIS is agreeable to providing MITSUI with said trade secret information, data, and know-how upon the terms and conditions as stated hereinafter;

NOW, THEREFORE, in consideration of the foregoing premises and the mutual covenants recited herein, the parties hereto agree as follows:

1. "Confidential Information", as used herein, means any and all information relating to the PRODUCT, whether written or graphic, furnished by DAVIS to MITSUI, either directly or indirectly, with the exception only of the following:

(a) information that as of the date of receipt by MITSUI is publicly available or subsequently becomes publicly available without fault on the part of MITSUI;

(b) information that at the time of receipt by MITSUI was actually known to it from its own sources;

(c) information that at any time is received in good faith by MITSUI from a third party that was lawfully in possession of the same and had the right to disclose the same; and

(d) information that the parties hereto mutually agree to release from the terms of this Agreement.

2. Promptly following execution of this Agreement, DAVIS shall provide MITSUI with such information that DAVIS has in its possession relating to the PRODUCT as may be necessary and sufficient for MITSUI to determine its commercial interest therein.

3. MITSUI agrees to receive and maintain in confidence all Confidential Information. In this regard, MITSUI agrees to disclose Confidential Information to no one other than its officers and employees or governmental regulatory officials who are directly concerned with its evaluation, and shall take all reasonable precautions to prevent the disclosure of Confidential Information to any unauthorized person, firm, or company. Upon disclosing Confidential Information to its officers and employees or governmental regulatory officials, MITSUI shall advise said officers and employees of the confidential nature thereof, and shall use reasonable efforts to prevent the unauthorized disclosure of such information by such officers and employees.

h.o.

4. MITSUI agrees not to use Confidential Information for any purpose other than the evaluation referred to in Paragraph 2. above without first obtaining the express written consent of DAVIS to do so or except pursuant to a further contractual arrangement between MITSUI and DAVIS .

5. In the event MITSUI does not wish to pursue PRODUCT following its review, MITSUI, at DAVIS' request, shall return all Confidential Information to DAVIS .

6. It is understood and agreed that the obligations of MITSUI under this agreement shall continue for a period of five (5) years from the date hereof, at the expiration of which period such obligations shall terminate.

IN WITNESS WHEREOF, each party hereto has caused this instrument to be executed, in duplicate, by its duly authorized representative as of the date first above written.

MITSUI PHARMACEUTICALS, INC.

By Fukuichi Oka
Fukuichi Oka

Title General Manager
New Product Planning

Date November 24, 1987

By Bonnie Davis
DR. BONNIE DAVIS

Date Dec 17, 1987

EXHIBIT 4

MITSUI
PHARMACEUTICALS, INC.
● 12-2, Nihonbashi 3-chome Chuo-ku Tokyo, 103 Japan ● (The 6th floor of Asahi Building)
● Telephone:(Tokyo) 274-4711 ~ 5 ● Cable: Mitsuipharm Tokyo ● Telex: 0222-3622(2223622 MITCHEM)

Our Ref. No. 2426

April 28, 1988

Dr. Bonnie M. Davis
17 Seacrest Drive
Huntington, NY 11743
U. S. A.

Dear Dr. Davis,

Thank you for your letter of April 13th, 1988 addressed to Mr. Oka together with the confidential information on your compound, galanthamine.

Since I have already transmitted to our research people for their first step evaluation, I will inform you of our attitude as soon as I receive any reaction from them.

By the way, as I am also in a position of licensing and acquisition of new products, I will get in touch with you from now on.

Thank you very much for giving us a chance of studying the detailed information on galanthamine.

With best regards,

Yours sincerely,

MITSUI PHARMACEUTICALS, INC.

Takafumi Kitano

Takafumi Kitano Ph.D.
Manager
New Product Planning Dept.

c.c.: Mr. Hattori, Mitsui & Co., New York
Mr. K. Kataoka, Mitsui & Co., Tokyo
F. Oka

EXHIBIT 5

17 Seacrest Drive
Huntington, New York 11743
Tel. (516) 423-3182
Fax (516) 423-3199
November 2, 1988

Takafumi Kitano, Ph.D.
Manager, New Product Planning Dept.
Mitsui Pharmaceuticals, Inc.
12-2, Nihonbashi 3-chome, Chuo-ku
Tokyo, 103 Japan
(6th Floor, Asahi Bldg.)

Mitsui Ref. No. 2426 (4/28/88)
2235 (10/13/87)

Dear Dr. Kitano,

Thank you for your letter of April 28, 1988 acknowledging receipt of confidential information on galanthamine.

How is your evaluation proceeding? I am enclosing two further abstracts to be presented at the Neuroscience conference in Toronto this month demonstrating galanthamine's efficacy in animal models of Alzheimer's disease. In addition, a revised copy of "Galanthamine for Alzheimer's Disease and Related Dementias" is included. This version reviews the poor clinical results seen when direct cholinergic agonists have been tried for Alzheimer's disease, and the positive results of a large ongoing study of THA, an acetylcholinesterase inhibitor comparable to galanthamine, but much more toxic. I hope that this information will be useful.

Discussions concerning the licensing of galanthamine are in progress. Some of these will involve the distribution of galanthamine or its analogs in Japan by multinational corporations. I believe that individual national corporations may function more efficiently, and have been told that Mitsui is highly respected. I would therefore look forward to the opportunity to work with you.

Can you advise me of the status of your evaluation?

Thank you very much for your consideration.

With best regards,

Yours sincerely,

Bonnie M. Davis, M.D.

c.c.: Mr. Hattori, Mitsui & Co., New York

EXHIBIT 6

MITSUI
PHARMACEUTICALS, INC.
● 12-2, Nihonbashi 3-chome Chuo-ku Tokyo, 103 Japan ● (The 6th floor of Asahi Building)
● Telephone(Tokyo) 274-4711~5 ● Cable: Mitsupharm Tokyo ● Telex: 0222-3622(2223622 MTCI)(FM)

Our Ref. No. 0017

February 3, 1989

Dr. Bonnie M. Davis
17 Seacrest Drive
Huntington
New York 11743
U. S. A.

Re: Galanthamine

Dear Dr. Davis,

I apologize you a long delay of our reply for the evaluation of the captioned compound. On your esteemed compound galanthamine our research groups for the evaluation of Alzheimer's disease area carefully studied the confidential information and the additional information presented to us on April 13 and November 2, 1988, respectively.

Though our research scientists are keeping a high interest in this compound from an academic point of view, our clinical development staffs emphasized that it is generally believed that regarding such sort of drugs there is quitely poor relation between animal data and clinical efficacy in patients with Alzheimer's disease and therefore, clinical studies of such drugs bring to us a difficulty of estimation of our reseach and development schedule and expense to proceed with the further development. Moreover, they are afraid that unexpected adverse effects may occur in patients during a long term treatment because of a similarity of its chemical structure to codein.

... Cont'd

MITSUI
PHARMACEUTICALS, INC.

Our Ref. No. 0017
2

As a result, to be frank, we reached a negative conclusion to take up your compound and I regret my response could not be more favorable to you.

Enclosed are the confidential documents you provided and we greatly appreciate your kind cooperation in giving us an opportunity of studying your compound and sincerely hope to have another chance of collaboration with you in the future.

With best regards.

Sincerely yours,

MITSUI PHARMACEUTICALS, INC.

Takafumi Kitano Ph. D.
Manager
New Product Plannig Dept.

Encl.

c.c.: Mr. M. Hattori, Mitsui & Co., New York
Mr. K. Kataoka, Mitsui & Co., Tokyo

CERTIFICATE OF SERVICE

I hereby certify that on the 2nd day of June, 2006, the attached **NOTICE OF DEPOSITION AND SUBPOENA OF MITSUI & CO (USA), INC. PURSUANT TO FEDERAL RULE OF CIVIL PROCEDURE 45** was served upon the below-named counsel of record at the address and in the manner indicated:

John W. Shaw, Esquire — HAND DELIVERY
Young Conaway Stargatt & Taylor, LLP
The Brandywine Building
1000 West Street, 17th Floor
Wilmington, DE 19801

Daniel F. Attridge, P.C. — VIA FEDERAL EXPRESS
Kirkland & Ellis LLP
655 15th Street, N.W.
Washington, DC 20005-5793

Mary B. Matterer, Esquire — HAND DELIVERY
Morris James Hitchens & Williams LLP
222 Delaware Avenue, 10th Floor
Wilmington, DE 19801

William A. Rakoczy, Esquire — VIA FEDERAL EXPRESS
Rakoczy Molino Mazzochi Siwik LLP
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Caesar, Rivise, Bernstein, Cohen & Pokotilow, Ltd.
1635 Market Street, 12th Floor
Philadelphia, PA 19103

VIA FEDERAL EXPRESS

/s/ Tiffany Geyer Lydon

Tiffany Geyer Lydon